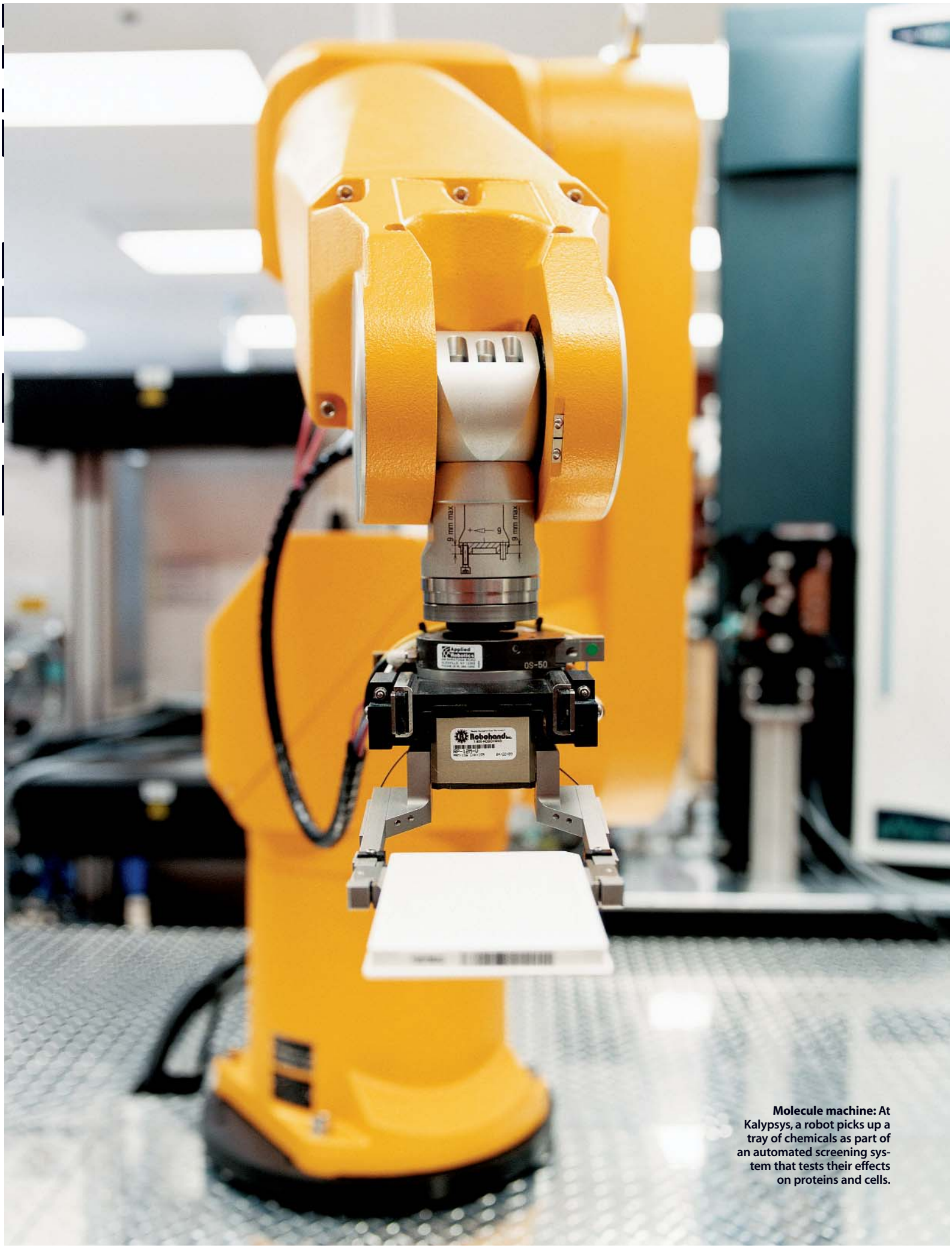
BRIDGING THE GENOMIC DIVIDE

WITH A MULTIMILLION-DOLLAR INITIATIVE, THE NATIONAL INSTITUTES OF HEALTH SEEK TO CLOSE THE GAP BETWEEN CUTTING-EDGE GENOMIC SCIENCE AND TRADITIONAL DRUG DEVELOPMENT. CENTRAL TO THE EFFORT: PUTTING INDUSTRIAL SCREENING TECHNOLOGIES IN THE HANDS OF ACADEMIC RESEARCHERS.

BY GREGORY T. HUANG PHOTOGRAPH BY DAVE LAURIDSEN

IT HAS BEEN THE MANTRA of genomics researchers for nearly 20 years now: understanding the genome will yield better and more affordable drugs that will cure even the deadliest diseases. But in the thick of this much ballyhooed genomic revolution, newcomers to the pharmacy shelf are few and far between and seem to offer (with a handful of notable exceptions) only trivially new ways to lower cholesterol and boost sex lives. Why? After all, researchers have in hand a draft of the human genome, the parts list for the hundreds of thousands of proteins that carry out the body's biological business. And they have already discerned that hundreds of those proteins—ones that go awry in cancer, for instance—would make obvious targets for new drugs. ▪ The problem is that there's a yawning gap between traditional pharmaceutical companies and genomics research. Genomics, still largely an academic pursuit, might divulge a specific protein's role in cell division, say, and what chemical probe blocks the protein's action. That may be important for understanding how tumors grow, but it is years away from where the pharmaceutical industry would begin developing a new cancer drug. In practice, most companies avoid novel targets because they are unproven, tied to unwanted effects downstream, or just too hard to hit with familiar drug compounds. The result: a no man's land of unpursued protein targets, half-baked chemical probes, and what-might-have-been drugs.



Molecule machine: At Kalypsys, a robot picks up a tray of chemicals as part of an automated screening system that tests their effects on proteins and cells.

Drug tester: John McKearn, president of Kalypsys, in front of a library of potential drug candidates.

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What could help bridge this gap is the emerging science of chemical genomics, which uses vast libraries of "small molecules"—synthetic compounds that bind to proteins and alter their functions—to probe how all the proteins encoded by the genome work in concert. Small molecules, it turns out, are a big deal for drug companies, too. From 1980 to 2003, 90 percent of new drugs approved by the U.S. Food and Drug Administration were made from small molecules. From aspirin to allergy pills, most small-molecule drugs are cheap and easy to produce—in stark contrast to the protein-based and other "large molecule" drugs on which biotech companies tend to place their bets. Combining the convenience of small-molecule drugs with the intelligence of genomic science could revitalize the lumbering drug industry and greatly improve health care.

LIBRARY SCIENCE

For Christopher Austin at Merck, it began with a simple question: "Chris, how would you like to come help us figure out what to do with the genome?" The proposition came from Francis Collins, who as director of the National Human Genome Research Institute at the National Institutes of Health (NIH) had led the effort to complete the Human Genome Project. It was mid-2002.

Austin, then director of genomic neuroscience at Merck Research Laboratories, jumped at the opportunity. This would be a chance to take a leading role in translating genomic research and new drug targets into novel, more effective therapies. "The genome presents an enormous problem, if you're a pharmaceutical company," Austin explains. "The failure rate is higher if you take on unprecedented targets." That's why drug companies tend to focus on a narrow set of targets and compounds they already understand.

In an effort to broaden the playing field, NIH announced in June that it is opening a Chemical Genomics Center. Headed by Austin, the center is part of a four-year "molecular libraries" initiative whose $32 million annual budget is expected to grow to about $100 million. The plan: to fund a nationwide network of centers to screen small molecules for their effects on cells and proteins and aggregate the results in a public database. "If we can populate the scientific literature with data on small molecules," Collins says, "that could set off light bulbs towards therapies that wouldn't otherwise happen."

Until now, most academics have not had access to the industrial-strength technologies required to synthesize and screen small molecules. And drug companies don't share data on their compounds. The hope is that, with this effort, academics will systematically explore small molecules, and drug companies will use the public results to better fight cancer, diabetes, and rare diseases that they currently have little financial incentive to pursue.

To jump-start the initiative, Collins and Austin signed a deal worth up to $30 million to license a molecular-screening system from Kalypsys, a San Diego, CA, startup. The system represents the state of the art in combinatorial chemistry for making small molecules, the hardware for screening them, and the informatics software for analyzing the results. More broadly, it represents an important step in turning the science of chemical genomics into practical technology that companies and research groups can use. "In terms of technology development," says Austin, "we are about where the Human Genome Project was in 1988"—two years after the invention of the automated DNA sequencer. But chemical genomics is vastly more complicated, he says. "This will make DNA sequencing look like child's play."

THROUGH THE SCREEN DOOR

Sitting in the Kalypsys boardroom, dressed all in black despite the summer weather, John McKearn says he used to be a serial killer—of drug candidates. The company's president and chief scientific officer is talking about the problem he saw during his stint at Pharmacia, the Peapack, NJ, pharmaceutical company acquired by drug giant Pfizer in 2003. According to McKearn, companies test thousands of candidates in series, wasting precious time and money on one compound only to find that it fails in some respect and then moving on to test another. To survive, McKearn says, drug companies must learn to screen compounds in parallel and to kill, or reject, the unpromising ones as early as possible. That's what Kalypsys aims to do.

The bottom line: McKearn predicts that Kalypsys's technology can shave 50 percent off the time and cost of traditional drug development. Considering that drug companies average $800 million in R&D investment for each compound that receives FDA approval, that's no idle boast. McKearn points out that Kalypsys took only six months to discover new anti-inflammatory drug candidates in animals—a process he says would take most drug companies two to three years—and plans to seek the FDA's permission to test its first drug on people in 2005. But of course, "the proof of the pudding is in the eating," says Janice Reichert, senior research fellow at the Tufts Center for the Study of Drug Development. "They have a good system, but it's not revolutionary."

Not yet, at least. Indeed, translating the latest biology into new small-molecule drugs has universally proven difficult. "Pharma [the pharmaceutical industry] is unprepared for the post-genomic age," McKearn says. The numbers game is daunting. Consider that the 30,000 genes in the human genome code for the activity of roughly 200,000 proteins. So far, scientists have discovered small molecules that interact in a predictable way with only about 500 proteins.

DAVE LAURIDSEN (MCKEARN); DAVID DEAL (COLLINS)

"HOW DO YOU MAKE FUNCTIONAL AND THERAPEUTIC SENSE OF THE WHOLE HUMAN GENOME? IT TAKES TIME AND CAPITAL. ACADEMIA HAS TIME BUT LACKS CAPITAL. PHARMA HAS CAPITAL BUT NO TIME." —CHRISTOPHER AUSTIN

Kalypsys's technology could change that. Walking up to a thick door near the company's main entrance, McKearn touches his index finger to a fingerprint scanner and swipes his identification badge through the door reader. Where McKearn's face should be, the badge has a picture of Dr. Evil from the Austin Powers films, a nod to McKearn's "evil plan" to disrupt traditional drug discovery and outcompete large drug companies. Inside the room are three large yellow robot arms standing at attention. Every few seconds, one of the robots springs to life, using a mechanical gripper to lift a small tray of chemicals out of a storage unit and swiveling to stack it at the next testing station.

On this day, the machines are doing tests on blood cells from leukemia patients and proteins suspected to be involved in the disease. One robot gathers 9-by-13-centimeter trays, dispensing samples—some proteins, some whole cells—into 1,536 tiny wells. The samples have been designed or modified to fluoresce when a protein's activity is altered or there is a physical change in a cell. In another set of trays are small molecules, which a second robot squirts into the samples; it puts the resulting mixtures into an incubator. After the prescribed incubation time, the third robot picks up the test mixtures and places them in an optical chamber, where they are examined by highly sensitive cameras. A central computer coordinates the robots and records the results of the tests.

The system allows the researchers to investigate a wide range of compounds and targets—and kill off dead ends—fast. "We were quite impressed," says NIH's Collins. For one thing, only one person needs to be present to start the machine, as opposed to the dozens of workers needed to run most big screening systems. The system operates day and night, screening a million compounds every day, which is more than many large drug companies can do.

After a long day, Simon Tisminezky, Kalypsys's business development manager, leads a tour of the company's manufacturing plant, a few kilometers away. This is where Kalypsys is building next-generation screening machines for itself, NIH, and a few other customers; it delivered a similar system to Merck in mid-2004. The facility, a cross between an airplane hangar and an auto mechanic's garage, is dark and empty after hours. So far, workers have completed incubators and storage units for the NIH system. By winter, Kalypsys plans to have a complete robotic system up and running; engineers will test the whole platform, then take it apart and ship it to NIH piece by piece.

Because its business plan calls for this sort of technology transfer, Kalypsys is building more than a machine: it's building a gateway between basic research and drug development. It will give a new community of scientists unparalleled access to the world's most advanced tools for probing the genome. Those tools could eventually change the way science *and* drug discovery are done. After the tour, Tisminezky is careful to set the security alarm as he leaves the facility and steps out into the setting sun.

NEW GENES, NEW DRUGS

If Kalypsys is building the gateway, then NIH is the gatekeeper. From the fourth floor of NIH's building 31, Francis Collins's office looks out over the institute's tree-lined campus in Bethesda, MD. It is a sweltering August day. Pictures of Collins and his family, his diplomas, and countless awards line the walls and shelves. But Collins is nowhere to be found.

It seems he has passed the day-to-day direction of what could be called the Human Genome Project, Act Two, to his deputies. In walks the Chemical Genomics Center's Austin with Jim Inglese, who is second in command and likewise a former Merck researcher. In a dress shirt and slacks, Austin has a casual air that belies the depth of his experience in genomics and drug discovery. He makes football analogies about where the "handoff" should occur between academic research and industrial drug development. He refers to Collins as "king" and "big guy." He jokes that he chose Kalypsys because of the San Diego weather.

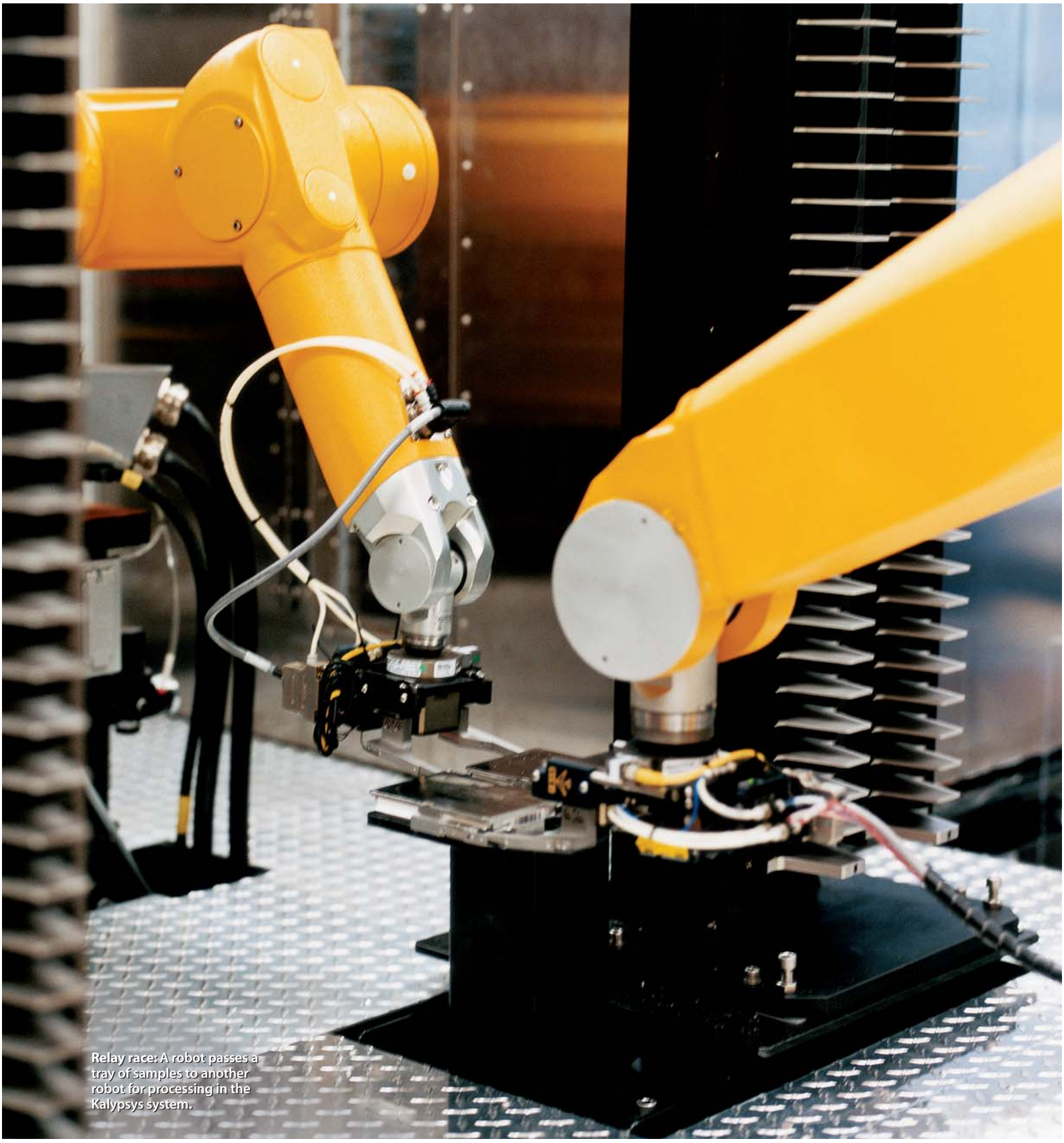
When the talk turns to the NIH initiative, though, Austin is all business, armed with charts and timelines to make his points. "The question of the day is, how do you make functional and therapeutic sense of the whole human genome?" he says. "It takes time and capital. Academia has time but lacks capital. Pharma has capital but no time." The right technology, he says, could change the terms of that equation. Once the NIH-funded network is up and running (Austin plans to fund five or six centers by next year), academic groups will compete for the opportunity to use the Kalypsys machines and other screening technologies—gaining capabilities previously reserved to industry.

That could lead to a wider variety of drug compounds for industry to work on, says Inglese, an expert on biomolecular screening. Instead of chasing frivolous cash cows like anti-impotence pills, companies might be able to derive huge benefits from developing treatments for cancer, diseases of the immune system, and other ailments. And because the new drugs will be based on small molecules, scientists know they will work, instead of knowing that they *should* work, as is the case with many large-molecule biotech drugs in development.

But Austin and Inglese bristle at the suggestion that their initiative signals a government move into drug development. They maintain that companies will still do the vast majority of the work needed to refine and develop drugs. Instead, what the NIH effort seems to demonstrate is that the border between basic science and technology development is shifting. Perhaps that shift is overdue; the biotech industry, for one, has suffered from premature efforts to translate molecular biology into useful therapies.

Whatever the implications, this follow-up to the genome project is near and dear to Collins. Big questions remain, he says: "How does the one-dimensional genome function in four-dimensional space and time? How does that go wrong? What can

DAVID DEAL (AUSTIN); DAVE LAURIDSEN (RELAY RACE)



Relay race: A robot passes a tray of samples to another robot for processing in the Kalypsys system.

be done to fix it?" Asked to predict how the effort will play out, Collins answers as both a scientist and a physician. "In a decade, we'll learn a substantial amount about how genes work together and how a cell does what it does," he says. "We'll understand the hereditary contribution to diseases such as diabetes and mental illness."

Will this new marriage of genomic science and drug discovery be a happy one? What bodes well for it is that, ultimately, the two disciplines have a common goal. Back at Kalypsys, McKearn is gathering himself for an off-site meeting. One might ask, in the end, what is really special about what he's doing. "The end customer for us is the patient," he says. "We can touch the lives of millions of people in a way that's unparalleled. That's what's keeping us going. We're not in it for the glory. It's a quest."

Gregory T. Huang is a *TR* associate editor.